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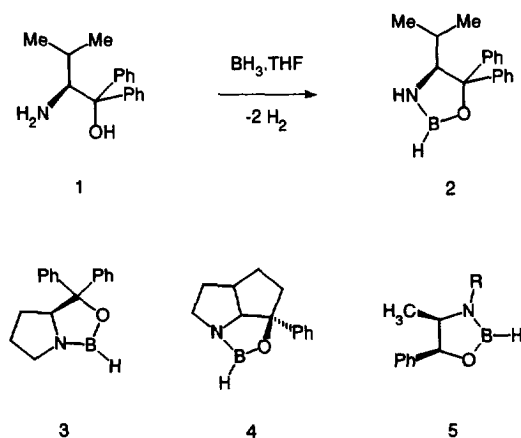
## Synthesis and Application of New Chiral Ligands for the Asymmetric Borane Reduction of Prochiral Ketones

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**Abstract:** Two chiral nonracemic  $\gamma$ -amino alcohols, ephedrine thiol and the corresponding (thio)-phosphoramidates and (thio)-phosphinamides have been examined as catalysts for the reduction of propiophenone by various boranes. Up to 95% *e.e.* can be obtained with the phosphorus derivatives. Copyright © 1996 Elsevier Science Ltd

Homogeneous enantioselective catalysis with *sub*-stoichiometric amounts of non-racemic chiral auxiliaries has received intense interest during the past several years. In particular, the enantioselective reductions of prochiral ketones to afford enantiomerically pure alcohols have been extensively investigated.<sup>1</sup> Fiaud and Kagan<sup>2</sup> were the first to recognize the potential of optically active borane complexes for these reductions, although the enantioselectivities obtained were only small. Hirao and co-workers<sup>3</sup> reported the first effective stereoselective borane reduction, using stoichiometric amounts of *in situ* prepared 1,3,2-oxazaborolidines **2** based on nonracemic chiral  $\beta$ -amino alcohols **1** (Scheme 1). It soon became apparent that such ligands could also be used catalytically.

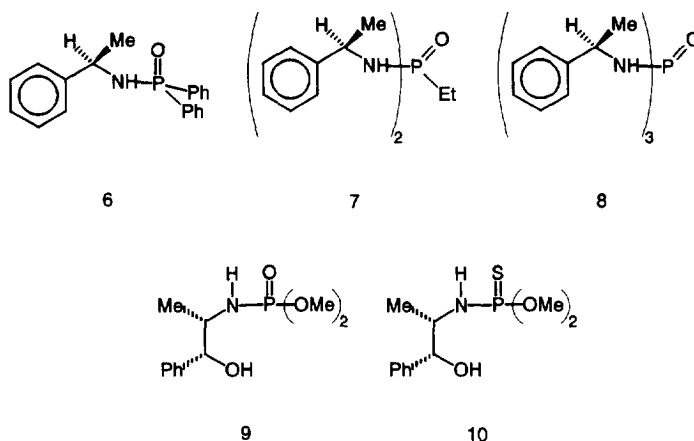


Scheme 1 Preparation and examples of 1,3,2-oxazaborolidines as ligand for borane reductions

Most of the oxazaborolidines used so far are formed from a  $\beta$ -amino alcohol moiety, *e.g.* ligands **3** and **4**

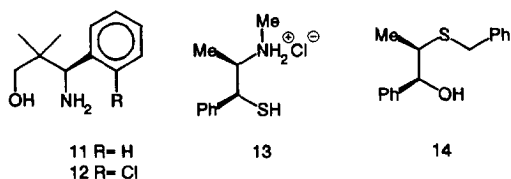
introduced by Corey and co-workers<sup>4</sup> or (1*R*,2*S*)-ephedrine **5**<sup>5</sup> (Scheme 1). These amino alcohols afford a suitable and relatively stable complexing site for the first boron involved in the reduction sequence,<sup>6</sup> although diols, diamines and amino acid containing ligands have also been reported to carry out this function.<sup>7</sup>

Wills and co-workers<sup>8</sup> reported the successful replacement of the  $\beta$ -amino alcohol functionality by  $N$ - $P=O$  containing ligands **6-8** for the asymmetric reduction of ketones using  $BH_3 \cdot SMe_2$  as reducing agent, although the obtained *e.e.*'s were rather disappointing. The perspectives of  $N$ - $P=O$  as ligand were further improved with the reports of Soai and co-workers<sup>9</sup> who were able to increase both yield and *e.e.* of the diethylzinc addition to aldehydes by conversion of several ephedra based ligands into the corresponding (thio)-phosphoramidates **9** and (thio)-phosphinamides **10** (Scheme 2).



Scheme 2 Several phosphorus containing catalytically active ligands

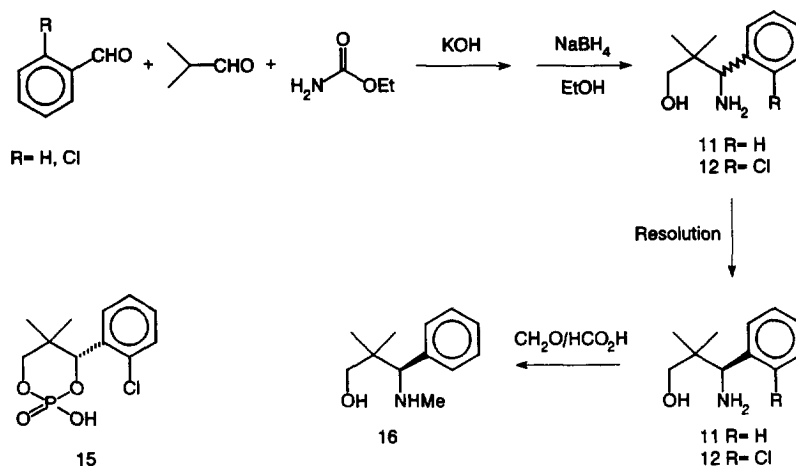
We have recently been engaged in the application of two structurally divergent types of compounds, namely 1-aryl-2,2-dimethyl-1,3-propanediols<sup>10</sup> (not shown) and the corresponding amino alcohols<sup>11</sup> **11** and **12** and thiol derivatives of ephedrine **13** and pseudoephedrine<sup>12</sup> (Scheme 3).



Scheme 3 Compounds used in present work

We find that **11** and **12** as well as **13** can be phosphorylated and that the products can be efficient ligands in the borohydride mediated reduction of propiophenone.<sup>13</sup>

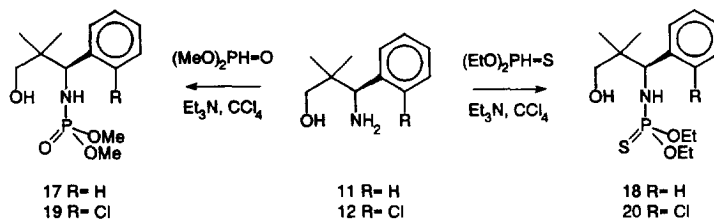
Synthesis of **11** and **12** was carried out according to the methodology described by ten Hoeve and Wynberg starting from benzaldehyde, isobutyraldehyde and ethyl carbamate.<sup>11</sup> Subsequent reduction of the *in situ* formed aldehyde (not shown) followed by facile resolution with phosphoric acid **15**<sup>10</sup> provides both enantiomers of the  $\gamma$ -amino alcohols<sup>14,15</sup> in moderate yield (Scheme 4).



Scheme 4 Synthesis and resolution of ligands **10** and **11**

Subsequent methylation of **11** using Eschweiler-Clark reaction conditions afforded the mono-methylated ligand **16** in 50% yield after sublimation<sup>16</sup> (Scheme 4). The sulfur containing ligand **14** was prepared from ephedrine according to the methods previously reported.<sup>17</sup>

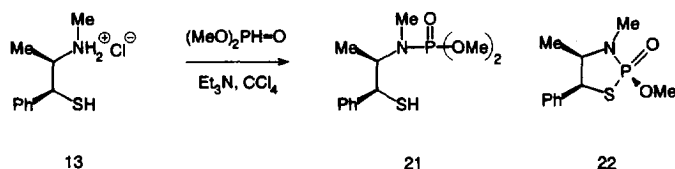
The corresponding phosphorus derivatives **17-20** were prepared by reaction of the amino alcohol with chlorophosphate or chlorothiophosphate employing basic conditions ( $\text{Et}_3\text{N}$  or pyridine). Alternatively, as illustrated in Scheme 5, stable (thio)-phosphonates were used, which were converted *in situ* into the trichloromethyl esters by means of reaction with  $\text{Et}_3\text{N}$  or pyridine and  $\text{CCl}_4$ ,<sup>18,19</sup> subsequent reaction with amino alcohol afforded the corresponding phosphorus ligands **17-20** in excellent yields (Scheme 5).



Scheme 5 Synthesis of phosphorus ligands **17-20**

No cyclized products were formed, except for *thio*ephedrine **13**, which gave polymeric products with chloro(thio)phosphates and a 50-50 mixture of desired and cyclized products with diethylthiophos-

phonate.<sup>20</sup> Reaction with dimethylphosphonate, however, afforded ligand **21** in 95% purity; it was not possible to remove the last 5% of cyclized product **22**<sup>21</sup> (Scheme 6). Clearly, compared to alcohols, thiols are more reactive under the employed reaction conditions, especially towards the less selective *thio*-phosphorus reagents.



Scheme 6 Synthesis of ligand **21** contaminated with **22**

As expected, derivatization via the trichloromethyl esters leads exclusively to amino phosphorylation, which point was verified from the <sup>31</sup>P NMR chemical shifts: downfield shifts were observed compared to the corresponding phosphonates.<sup>22</sup>

The phosphorus ligands **17–20** gave rise to extremely complicated <sup>1</sup>H NMR spectra, not only because of extensive phosphorus coupling but also due to diastereotopism of nearly all the protons in these molecules, as is seen in the <sup>1</sup>H NMR spectrum of ligand **20** (Figure 1).

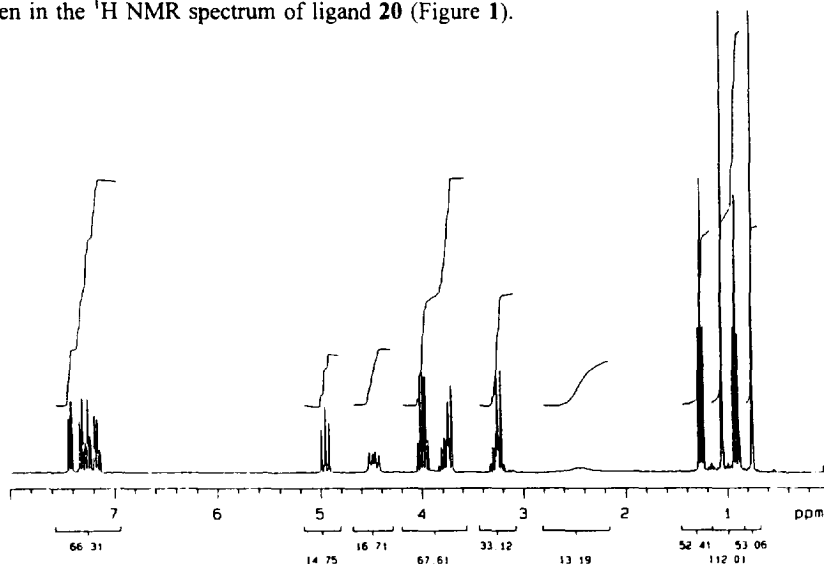


Figure 1 <sup>1</sup>H NMR spectrum of ligand **20** recorded in CDCl<sub>3</sub> ([L] = 0.01 M)

This spectrum provides unambiguous evidence for phosphorylation at the amino group; the amino proton shows an appreciable coupling due to the phosphorus nucleus and a coupling with the benzylic proton. This is most clearly seen in the 2D COSY spectrum (Figure 2). The amino proton forms a strong hydrogen

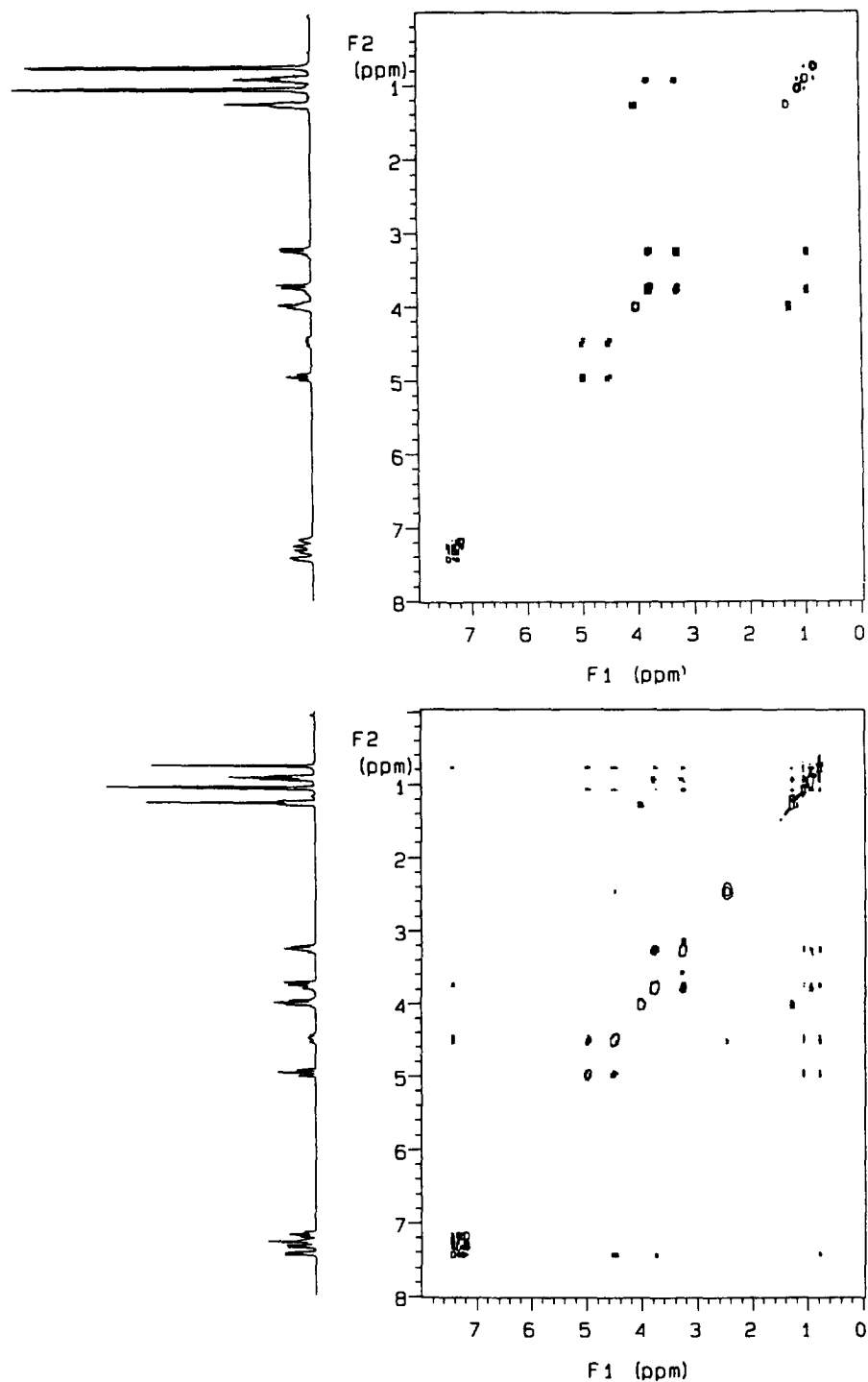
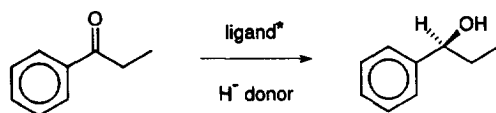


Figure 2 COSY (upper) and NOESY (lower) spectra of ligand 20 recorded in CDCl<sub>3</sub> ([L]= 0.01 M).

bridge with the alcohol, as can be seen by a strong NOE interaction. The rotational freedom must be greatly restricted. This leads to the observed strong diastereotopism of the two methylene groups of the ethyl ester units and the additional, extreme, diastereotopism within one of the ethyl groups, which is clearly observed in the 2D COSY spectrum. The  $^1\text{H}$  NMR spectra were highly sensitive to concentration effects and (small) impurities like *e.g.* traces of water.

We find that these ligands catalyse the borane mediated reduction of propiophenone<sup>23</sup> to afford 1-phenylpropanol in both excellent yield and enantiomeric excess (Scheme 7). In order to gain insight in the factors governing stereodifferentiation three borane complexes were used as hydride donor:  $\text{BH}_3\text{-THF}$  complex,  $\text{BH}_3\text{-SMe}_2$  complex and  $\text{LiBH}_4$ .



Scheme 7 Standard reduction of propiophenone using ligand and hydride donor (see text for explanation)

In practice, the active oxazaborolidines were prepared *in situ* by adding 6 mmol of hydride donor to a cooled ( $-20\text{ }^\circ\text{C}$ ) solution of ligand (0.1 mmol) in THF (10 mL). After stirring for 30 min., propiophenone (6 mmol) in 5 mL of THF was slowly added and the mixture was stirred for another 30 min. at  $-20\text{ }^\circ\text{C}$ . Acidic workup afforded 1-phenylpropanol, which was analyzed by means of chiral GC or NMR.<sup>24</sup> The results are collected in Table 1.

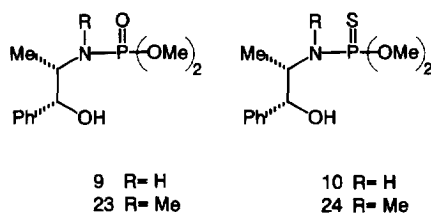
ligand	$\text{BH}_3\text{-THF}$	$\text{BH}_3\text{-SMe}_2$	$\text{LiBH}_4$
11	39 <i>R</i> (83)	38 <i>R</i> (84)	87 <i>S</i> (95)
12	34 <i>R</i> (69)	25 <i>R</i> (75)	58 <i>S</i> (95)
13	62 <i>S</i> (73)	52 <i>S</i> (82)	78 <i>S</i> (95)
14	- <sup>a</sup>	- <sup>a</sup>	- <sup>a</sup>
16	38 <i>S</i> (76)	22 <i>S</i> (89)	27 <i>S</i> (95)
17	91 <i>S</i> (79)	63 <i>S</i> (80)	89 <i>S</i> (95)
18	93 <i>S</i> (81)	82 <i>S</i> (82)	81 <i>S</i> (95)
19	75 <i>S</i> (74)	49 <i>S</i> (75)	61 <i>S</i> (77)
20	77 <i>S</i> (71)	56 <i>S</i> (74)	76 <i>S</i> (92)
21	95 <i>S</i> (87)	53 <i>S</i> (74)	89 <i>S</i> (95)

Table 1 Enantiomeric excesses, configuration and conversions (%) of borane mediated catalytic reductions. <sup>a</sup> Only racemic material was obtained

Firstly, ligands **11**, **12**, **13**, **14** and **16** were compared. Ligand **13** yields 1-phenylpropanol in good ( $\text{BH}_3\cdot\text{THF}$  and  $\text{BH}_3\cdot\text{SMe}_2$ ) to excellent ( $\text{LiBH}_4$ ) yields; the *e.e.*'s are 62, 52 and 78%, respectively (*S*). Although **13** has proven to be a better ligand than ephedrine in diethylzinc addition reactions,<sup>13</sup> the results in the borane reductions are about comparable. Ligand **12** gives 1-phenylpropanol in moderate yields, except for the reduction with  $\text{LiBH}_4$  (> 95%); the obtained *e.e.*'s are moderate (58% max.,  $\text{LiBH}_4$ ). Ligand **11** gives high conversions in all the cases, again  $\text{LiBH}_4$  being the most efficient with a conversion of >95% and an *e.e.* of 87%. As for ligand **12**, the use of  $\text{BH}_3\cdot\text{THF}$  and  $\text{BH}_3\cdot\text{SMe}_2$  affords the *R* enantiomer of 1-phenylpropanol, whereas  $\text{LiBH}_4$  yields predominantly the *S* enantiomer! Ligand **16** gives the alcohol in high yields but only moderate *e.e.*'s (31% max.,  $\text{BH}_3\cdot\text{THF}$ ). Not unexpectedly, the use of sulfide **14** resulted only in racemic 1-phenylpropanol, formed by uncatalyzed reduction.

The phosphorus containing ligands proved to be able to induce both higher conversion and *e.e.* compared to the other ligands. With  $\text{LiBH}_4$  the highest conversions were obtained and with  $\text{BH}_3\cdot\text{THF}$  the highest *e.e.*'s (all *S*). For ligand **17** and **18**, the conversions typically ranged from 79 ( $\text{BH}_3\cdot\text{THF}$ ) to 95% ( $\text{LiBH}_4$ ); the thio-phosphorus ligand induced slightly higher *e.e.*'s (93 vs 91%,  $\text{BH}_3\cdot\text{THF}$ ). As for the nonphosphorus ligands, the chlorine containing ligands **19** and **20** gave both slightly lower conversions and *e.e.*'s (See Table 1 for details). Although ligand **21** could not be obtained in completely pure form, excellent results were obtained with  $\text{BH}_3\cdot\text{THF}$  (conv. 87%, *e.e.* 95%) and with  $\text{LiBH}_4$  (conv. >95%, *e.e.* 89%). Clearly, these results indicate that compared to **13** a much higher efficiency is obtained.

In order to make a comparison between (*1R,2S*)-norephedrine and the phosphorus containing equivalents, ligands **9** and **10** were prepared as well as the (*1R,2S*)-ephedrine equivalents **23** and **24** according to the protocol described (*vide supra*)(Scheme 8).



Scheme 8

Again, the thiophosphorus derivatives **23** and **24** are the most efficient catalysts (See Table 2). Although these results are slightly better than those described in the literature<sup>1</sup> for the ephedra, the effect of phosphorus is less dramatic compared to the ligands **17**-**20**.

We also performed the reactions using stoichiometric amounts of ligand and 2 equivalents of hydride donor. In all the cases conversions were less compared to the catalytic approach, whereas the obtained *e.e.*'s were dramatically lower; for some of the compounds (**13**, **12** and **20**) no *e.e.*'s were obtained at all! Also, isolation of the oxazaborolidines and subsequent use in the catalytic sequence gave no better results.



ligand	BH <sub>3</sub> .THF	BH <sub>3</sub> .SMe <sub>2</sub>	LiBH <sub>4</sub>
<b>9</b>	69 <i>S</i> (76)	44 <i>S</i> (82)	76 <i>S</i> (95)
<b>10</b>	74 <i>S</i> (79)	45 <i>S</i> (85)	78 <i>S</i> (95)
<b>23</b>	63 <i>S</i> (80)	39 <i>S</i> (77)	63 <i>S</i> (95)
<b>24</b>	77 <i>S</i> (81)	49 <i>S</i> (89)	74 <i>S</i> (95)

**Table 2** *Enantiomeric excesses, configuration and conversions (%) of borane mediated catalytic reductions*

It is clear, however, that by changing the borane hydride from BH<sub>3</sub>.THF to LiBH<sub>4</sub> using ligands **11** and **12** a reversal of stereodifferentiation takes place, indicating a probable change of mechanism. We do not feel that there is sufficient information available to postulate a stereochemical model of the transition state leading to reduction.

In conclusion, the newly introduced ligands offer unique possibilities to influence stereocontrol by simple structural modification. Using the methodology described, other phosphorus containing ligands are readily available and, moreover, have been shown to be efficient catalysts for borane mediated hydride reduction reactions of prochiral ketones. Other applications will be addressed in forthcoming manuscripts.<sup>25,26</sup>

## Experimental

### General Remarks

All solvents were dried according to literature procedures. All reactions were carried out under an argon atmosphere, using Schlenck line conditions. <sup>31</sup>P, <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian VXR 300 instrument thermostatted at 30 °C. The chemical shifts are expressed relative to CDCl<sub>3</sub> for <sup>1</sup>H NMR (at δ 7.26 ppm) or <sup>13</sup>C NMR (at δ 76.91 ppm) and to (NPCl<sub>2</sub>)<sub>3</sub> (at δ 19.91 ppm) for <sup>31</sup>P NMR spectra. Deuterated solvents were dried over an Al<sub>2</sub>O<sub>3</sub> (activity I) column just prior to use. BH<sub>3</sub>.THF and BH<sub>3</sub>.SMe<sub>2</sub> (both 1 molar in THF) and LiBH<sub>4</sub> (2 molar in THF) were obtained from Aldrich and Acros Chimica, respectively, and used as received. Materials not described here were prepared according to literature procedures.<sup>10,11,12,17</sup>

### (-)-*N*-Methyl-3-amino-3-phenyl-2,2-dimethyl-1-propanol **16**

A suspension of 5.3 g (30 mmol) (-)-amino alcohol **11** in 100 mL of 96% formic acid was cooled to 0 °C with vigorous stirring. To this solution was slowly added 100 mL of 37% formaldehyde and the reaction mixture was subsequently brought to reflux (80 °C) overnight. The mixture was cooled and made alkaline using 2 N NaOH solution. The mixture was extracted with diethyl ether (3 x 100 mL) and the combined ether layers were washed with water (100 mL) and brine (100 mL). After drying over anhydrous sodium sulfate, the solvent was evaporated *in vacuo*, yielding a sticky oil. Sublimation afforded **16** as white cubic crystals. Yield 2.90 g (15.01 mmol, 50%). Mp 51-53 °C; [α]<sub>D</sub><sup>20</sup> = -12.7 (c 0.01, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>):

0.63 (s, 3H), 1.04 (s, 3H), 1.89 (s, 3H), 2.79 (s, 1H), 3.31 (d,  $^2J_{AB}$  = 10.7 Hz, 1H), 3.62 (d,  $^3J$  = 7.7 Hz, 1H), 3.68 (d,  $^2J_{AB}$  = 10.7 Hz, 1H), 4.61 (d,  $^3J$  = 7.7 Hz, 1H), 7.2-7.3 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 20.43 ( $\text{CH}_3$ ), 23.15 ( $\text{CH}_3$ ), 38.22 ( $\text{CH}_3$ ), 78.15 (CH), 79.78 (C), 88.67 ( $\text{CH}_2$ ), 127.13 (CH), 127.49 (CH), 129.51 (CH), 137.95 (C); HRMS calcd for  $\text{C}_{12}\text{H}_{19}\text{NO}$  193.146, found 193.146.

*(-)-3-Amino-N-(O,O-dimethylphosphoryl)-3-phenyl-2,2-dimethyl-1-propanol 17*

A suspension of 5.0 g (27.93 mmol) (-)-amino alcohol **11**, 3.50 g (31.20 mmol) di-methylphosphonate and 5.0 mL of  $\text{Et}_3\text{N}$  in 5 mL of  $\text{CH}_2\text{Cl}_2$  was stirred and cooled to  $-10^\circ\text{C}$ . To this suspension was added very slowly 6.5 mL of  $\text{CCl}_4$  which resulted in an exothermic reaction. Stirring was continued for another 30 min., during which time the reaction was allowed to reach RT. After addition of 25 mL of  $\text{CH}_2\text{Cl}_2$  the crude mixture was washed with 2 N HCl solution (3 x 25 mL), saturated  $\text{NaHSO}_3$  solution (3 x 25 mL) and water (2 x 25 mL) and subsequently dried over  $\text{Na}_2\text{SO}_4$ . The residue was purified by means of column chromatography (silica gel, hexane/AcOEt 3/1). **17** was obtained as an oil, which solidified upon standing. The solid material was crystallized twice from AcOEt by slow addition of hexane. Yield 7.08 g (24.67 mmol, 88 %). Mp  $95-98^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{20}$  =  $-38.01$  (c 0.08, MeOH);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.72 (s, 3H), 0.99 (s, 3H), 3.01 (s, br, OH), 3.35 (d,  $^2J_{AB}$  = 11.35 Hz, 1H), 3.57 (d,  $^3J$  = 10.98 Hz, 3H), 3.74 (d,  $^3J$  = 7.69 Hz, 3H), 4.12 (d,  $^3J$  = 10.62 Hz, 1H), 4.14 (s, br, NH), 7.20-7.38 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 20.50 ( $\text{CH}_3$ ), 23.48 ( $\text{CH}_3$ ), 39.32 (d,  $^3J$  = 6.39 Hz, C), 52.85 (d,  $^2J$  = 4.78 Hz,  $\text{CH}_3$ ), 53.18 (CH), 61.54 ( $\text{CH}_3$ ), 69.28 ( $\text{CH}_2$ ), 127.03 (CH), 127.76 (CH), 127.92 (CH), 128.17 (CH), 141.18 (C);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 10.93 ppm; HRMS calcd for  $\text{C}_{13}\text{H}_{22}\text{NPO}_4$  287.128, found 269.118 ( $-\text{H}_2\text{O}$ ).

*(-)-3-Amino-N-(O,O-diethylthiophosphoryl)-3-phenyl-2,2-dimethyl-1-propanol 18*

Prepared as described for **17** from **11** and diethylthiophosphonate<sup>27</sup> in 85% yield.

Mp  $62-63^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{20}$  =  $-27.57$  (c 0.07, MeOH);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.72 (s, 3H), 0.88 (t,  $^3J$  = 6.96 Hz, 3H), 0.94 (s, 3H), 1.22 (t,  $^3J$  = 6.22 Hz, 3H), 2.32 (s, br, OH), 3.17 (d,  $^2J_{AB}$  = 11.35 Hz, 1H), 3.27 (ddq,  $^2J_{AB}$  = 15.02 Hz,  $^3J$  = 9.89 Hz,  $^3J$  = 6.96 Hz, 1H), 3.72 (d,  $^2J_{AB}$  = 11.35 Hz, 1H), 3.79 (ddq,  $^2J_{AB}$  = 15.02 Hz,  $^3J$  = 6.96 Hz,  $^3J$  = 2.93 Hz, 1H), 3.94 (m, 1H), 4.17 (d,  $^2J$  = 13.66 Hz, 1H), 4.31 (d,  $^3J$  = 10.98 Hz, 1H), 7.19-7.31 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 15.10 (d,  $^3J$  = 10.0 Hz,  $\text{CH}_3$ ), 15.59 (d,  $^3J$  = 8.54 Hz,  $\text{CH}_3$ ), 19.99 ( $\text{CH}_3$ ), 23.12 ( $\text{CH}_3$ ), 39.26 (C), 61.20 (d,  $^2J$  = 2.44 Hz, CH), 62.74 (d,  $^2J$  = 4.89 Hz,  $\text{CH}_2$ ), 63.91 (d,  $^2J$  = 4.88 Hz,  $\text{CH}_2$ ), 69.48 ( $\text{CH}_2$ ), 126.88 (CH), 127.59 (CH), 128.09 (CH), 140.89 (C);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 70.30 ppm; HRMS calcd 301.137, found 301.137.

*(-)-3-Amino-N-(O,O-dimethylphosphoryl)-3-(2-chlorophenyl)-2,2-dimethyl-1-propanol 19*

Prepared as described for **17** from **12** and dimethylphosphonate in 92% yield. The residue was purified by means of column chromatography (silica gel, hexane/AcOEt 2/1).

Mp  $75-77^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{20}$  =  $-17.01$  (c 0.1,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.71 (s, 3H), 1.13 (s, 3H), 3.21 (d,  $^3J$  = 11.35 Hz, 3H), 3.22 (d,  $^2J_{AB}$  = 11.34 Hz, 1H), 3.64 (d,  $^3J$  = 11.35 Hz, 3H), 3.74 (d,  $^2J_{AB}$  = 11.34 Hz, 1H), 4.76 (d,  $^3J$  = 3.29 Hz, 1H), 4.78 (d,  $^3J$  = 3.29 Hz, 1H), 7.12-7.55 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 20.70 ( $\text{CH}_3$ ), 23.47 ( $\text{CH}_3$ ), 40.20 (d,  $^3J$  = 6.10 Hz, C), 52.89 ( $\text{CH}_3$ ), 53.54 ( $\text{CH}_3$ ), 56.93 (CH), 69.56 ( $\text{CH}_2$ ), 126.77 (CH), 128.34 (CH), 129.43 (CH), 129.69 (CH), 134.15 (C), 139.91 (C);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 10.98 ppm; HRMS calcd for  $\text{C}_{13}\text{H}_{21}\text{PClNO}_4$  321.089, found 303.079 ( $-\text{H}_2\text{O}$ ).

**(-)-3-Amino-N-(O,O-diethylthiophosphoryl)-3-(2-chlorophenyl)-2,2-dimethyl-1-propanol 20**

Prepared as described for **17** from **12** and diethylthiophosphonate in 87% yield. The residue was purified by means of column chromatography (silica gel, hexane/AcOEt 2/1).

Mp 64-65 °C;  $[\alpha]_D^{20} = -5.51$  (c 0.07, MeOH);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 0.77 (s, 3H), 0.93 (t,  $^3J = 6.22$  Hz, 3H), 1.06 (s, 3H), 1.27 (t,  $^3J = 6.22$  Hz, 3H), 2.01 (s, br, OH), 3.24 (d,  $^2J_{AB} = 11.35$  Hz, 1H), 3.23 (ddq,  $^2J_{AB} = 9.89$  Hz,  $^3J = 7.33$  Hz,  $^3J = 6.22$  Hz, 1H), 3.74 (d,  $^2J_{AB} = 11.35$  Hz, 1H), 3.80 (ddq,  $^2J_{AB} = 9.89$  Hz,  $^3J = 6.22$  Hz,  $^3J = 2.93$  Hz, 1H), 4.01 (m, 1H), 4.42 (s, br, NH), 4.97 (d,  $^3J = 11.72$  Hz, 1H), 7.15-7.44 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 15.28 (d,  $^3J = 9.57$  Hz,  $\text{CH}_3$ ), 15.78 (d,  $^3J = 7.98$  Hz,  $\text{CH}_3$ ), 20.08 ( $\text{CH}_3$ ), 22.88 ( $\text{CH}_3$ ), 40.17 (d,  $^3J = 7.18$  Hz, C), 56.30 (d,  $^2J = 3.19$  Hz, CH), 62.78 (d,  $^2J = 3.99$  Hz,  $\text{CH}_2$ ), 63.26 (d,  $^2J = 5.59$  Hz,  $\text{CH}_2$ ), 69.57 ( $\text{CH}_2$ ), 126.53 (CH), 128.13 (CH), 129.21 (CH), 129.53 (CH), 133.94 (C), 139.45 (C);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 69.52 ppm; HRMS calcd 365.098, found 365.098.

**(1R,2S)-N-(O,O-Dimethylphosphoryl)thiolephedrine 21**

Prepared as described for **17** from (1R,2S)-thiolephedrine<sup>12</sup> **13** and dimethylphosphonate.

Purification by means of careful column chromatography (silicagel, hexane/AcOEt 90/9 containing a small amount of  $\text{Et}_3\text{N}$ ) afforded **21** contaminated with 5-10% **22**. We were unable to purify this material completely.

For **18**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.41 (d,  $^3J = 9.02$  Hz, 3H), 3.61 (d,  $^3J = 16.52$  Hz, 3H), 3.82 (m, 1H), 3.76 (d,  $^3J = 14.56$  Hz, 3H), 4.08 (m, 1H), 7.06-7.19 (m, 5H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 68.91 ppm; Due to cyclization no proper HRMS could be obtained.

For **19**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.04 (d,  $^3J = 6.59$  Hz, 3H), 2.94 (d,  $^2J = 1.35$  Hz, 3H), 3.30 (d,  $^3J = 4.57$  Hz, 3H), 4.02 (m, 1H), 5.05 (m, 1H), 7.21-7.37 (m, 5H);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ): 11.52 ppm; HRMS calcd 289.090, found 289.090.

**General procedure for stereoselective reduction**

Ligand (0.1 mmol) was dissolved in 10 mL of dry THF and cooled to -20 °C. At this temperature borane complex (6 mmol) was slowly added and the reaction mixture was stirred for 30 min. A solution of propiophenone (6 mmol) in THF (5 mL) was added over a period of 60 min. After addition, the mixture was stirred for another 30 min. at -20 °C and subsequently quenched by slow addition of 1 N HCl solution (5 mL). Extraction by means of diethyl ether afforded the crude alcohol. Enantiomeric excesses and conversions were determined using a Hewlett Packard 5890A chromatograph equipped with a 50 m. WCOT fused silica column coated with CP cyclodextrin- $\beta$ -2,3,6-M-19 (Chrompack no. 7501) and a Hewlett Packard HP 3396 series II integrator at 120 °C. Retention times (oven temp. 120 °C, flow 100 mL/min He): propiophenone 20.1 min., R-1-phenylpropanol 27.5 min. and S-1-phenylpropanol 28.2 min. Alternatively, an  $^{31}\text{P}$  NMR based *e.e.* determination was performed.<sup>23</sup>

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<sup>31</sup>P{NMR (CDCl<sub>3</sub>): 68.09 ppm.

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